January 2015

Non-Small Cell Lung Cancer In The National Cancer Database

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Non-Small Cell Lung Cancer in the National Cancer Database

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

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2015

Acknowledgements

I would like to acknowledge and thank all who helped, supported, and funded my thesis project at Yale University School of Medicine.

Firstly, I owe an extreme deal of gratitude to my thesis advisor, mentor, and principal investigator Dr. Daniel Boffa of the Department of Surgery at Yale School of Medicine. He generously guided, encouraged, and pushed me to make the most of my research experience. In addition, he went beyond the role of thesis advisor by mentoring me through the first and second year of medical school, my surgery clerkship, and helping me define my career goals.

I also am grateful to his colleagues in the Department of Surgery Drs. Anthony Kim and Frank Detterbeck for their support and recommendations of the projects included in my thesis. I would also like to thank Dr. Ursula Brewster in the Department of Nephrology for her support and mentorship in my deciding to continue my research project in the department of surgery despite my hopeful residency in internal medicine.

Thank you also to Joshua Rosen, Dr. Amy Moreno, and Dr. Alberto Antonicelli for their help, support and collaboration in my learning SAS, the intricacies of the NCDB, and the research contained in my thesis. I would also like to thank the Yale StatLab for their help.

I am also very grateful to the Members of the Ogilvie family for their generous contribution to Yale School of Medicine that made my attendance at Yale possible, as well as the Yale University School of Medicine Medical Student Research Grant I was awarded during the 2013-2014 school year.

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INTRODUCTION

In the United States, lung cancer remains the leading cause of cancer-related death for both men and women. The American Cancer Society estimates that in 2014, lung cancer represented over 25% of all cancer fatalities.[1]

The National Cancer Database (NCDB) is a hospital-based outcomes data resource that is estimated to capture 70% of newly diagnosed lung cancers in the United States. The NCDB is jointly sponsored by the American College of Surgeons and the American Cancer Society and represents the largest clinical oncology databases in the world.[2] The database has previously been used to study patterns of care and overall survival in different non-small cell lung cancer subsets (NSCLC), and the immense size and breadth also leaves the NCDB uniquely suited to study less common oncologic scenarios.

We chose to utilize the NCDB for two studies: First, we studied patterns of care of clinical stage IIIA-cN2 NSCLC patients to understand the management of this disease and the factors that influence treatment and outcomes. Second, we investigated the survival among incompletely resected NSCLC patients and attempted to identify the optimal response to positive surgical margins.

Management of Clinical Stage IIIA Primary Lung Cancers

The absence or presence of mediastinal lymph node metastases (N2 disease) is important to both the prognosis and management of NSCLC.[3] The optimal treatment response to the presence of N2-positive NSCLC is uncertain as data can be found to support both surgical and nonsurgical approaches.[4] Accurate clinical staging of the mediastinum is

very important, because the N2 designation typically differentiates these patients from early stages with better prognostic and entirely different treatment implications.[5] Unfortunately, the accuracy of the clinical staging of the mediastinum can be highly variable given that noninvasive staging techniques have false positive rates of 25% to 40%,[6] and invasive mediastinal staging is often done with varying frequency and effectiveness.[7] Therefore, the completeness of the clinical mediastinal staging evaluation should be considered a critical consideration to the management of NSCLC in the United States. We chose to study this controversial cohort in the NCDB in order to better understand assess how this situation is managed in the United States.

Impact of Adjuvant treatment for Microscopic Residual disease

Surgical resection with complete tumor removal (R0) is the standard of care for locoregionally confined NSCLC and is associated with the best survival for acceptable risk patients.[5] However, an estimated 6% of patients are left with microscopic (R1) or macroscopic (R2) disease at the surgical margin.[8,9] The presence of residual disease at the surgical margin is an established marker for compromised survival,[10-12] resulting in a decrease in 5-year survival of approximately 50%.[9]

Recognizing the negative prognostic implications of positive surgical margins, clinicians have employed a variety of adjuvant therapy approaches in hopes of extending survival. The fortunate the rarity of this scenario, however, has resulted in a lack of data and a paucity of concrete recommendations to guide clinicians in this situation. For example the National Comprehensive Cancer Network recommends a multitude of options for positive NSCLC surgical margins (re-resection alone, re-resection with adjuvant chemotherapy, adjuvant radiation therapy alone, or

adjuvant radiation therapy with adjuvant chemotherapy therapy).[13] These recommendations are based on a lower level of evidence (consensus, but not uniform within the committee, category 2B),[13,14] highlighting the lack of suitable primary or secondary evidence in this area.

Therefore, in our second study, we chose to analyze the longitudinal outcomes associated with various adjuvant therapies for incompletely resected NSCLC in the NCDB in order to identify the optimal management when faced with this challenging clinical problem.

METHODS

National Cancer Database

The NCDB is a hospital-based data resource founded in 1988 as a joint project of the American Cancer Society and Commission on Cancer. The NCDB captures patient, tumor, treatment, and longitudinal follow-up data for an estimated 70% of newly diagnosed cancer patients cared for by over 1400 hospitals in the United States. The NCDB maintains "the data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator."[2]

Study Population

Management of Clinical Stage IIIA Primary Lung Cancers

In accordance with our Institutional Review Board-approved clinical research protocol, the NCDB was queried for histologically confirmed non-small cell lung cancer (NSCLC)

patients age 19 years or greater, diagnosed and clinically staged between 1998 and 2011, representing the patient's first primary cancer (n = 760,484). Patients were further specified as being clinical stage III (5th and 6th editions of the American Joint Commission on Cancer staging manual) and T1-3, N2, and M0. Patients with missing data for treatment were excluded. The final patient population was 83,913.

Impact of Adjuvant treatment for Microscopic Residual disease

In accordance with our Institutional Review Board-approved clinical research protocol, treatment naïve (no preoperative chemotherapy or radiation) patients 19 years or older diagnosed with non-small cell lung cancer (NSCLC) as their first and only primary invasive cancer, between 2003 and 2006 were evaluated. Inclusion criteria consisted of NSCLC histology codes,[15] undergoing surgery (bronchial sleeve resection, wedge resection, segmental resection, lobectomy or bilobectomy, extended lobe or bilobectomy, pneumonectomy or extended pneumonectomy), and pathological stage I – III NSCLC.

Patients that received neoadjuvant chemotherapy or neoadjuvant radiation, hormone therapy, immunotherapy, or palliative care were excluded. Patients that died within 30 days of surgery were excluded because they would likely not have survived long enough to receive adjuvant therapy. Patients with missing data for treatment were excluded.

The final analytic cohort contained 54,512 patients. Of these, 51,410 patients were coded by the NCDB as “no residual tumor” (R0) at the surgical margins.[16] The NCDB considers “no residual tumor” to include cases where all surgical margins were grossly and microscopically negative after resection of the primary tumor. 3,102 patients in the population were classified as having an incomplete resection, of which 1,688 had

microscopic residual tumor (R1). Microscopic residual tumor is defined in the NCDB as residual disease that cannot be seen by the naked eye. 181 cases were coded as macroscopically residual tumor (R2), defined as gross tumor of the primary site that is visible to the naked eye. Additionally 1,233 of the 3,102 cases of incomplete resection were coded as "residual tumor, NOS" indicating that residual disease at the primary site was present following surgery, but further information is not available.

Study Variables

Study variables were analyzed as defined by the Participant User Data File dictionary (available at http://ncdbpufbeta.facs.org/?q=node/259).

The measures for education level, household income, and urban/rural status were determined for each patient's area of residence by matching the zip code of the patient at the time of diagnosis to 2000 US Census.[17] The NCDB represents comorbidity as a modified Charlson-Deyo score reflecting 15 comorbid conditions and classifies patients into three categories: 0, 1, and 2+.[18]

It was determined prior to analysis that "adjuvant" therapy would only include treatment that was given after surgery, but within 180 days of diagnosis (as treatment beyond this time point could reflect disease progression).

The adjuvant radiation therapy group was determined by using the NCDB's "Radiation Surgery Sequence" data item that specifies the temporal relationship of the radiation therapy to the primary surgical procedure. Cases in which radiation was coded as being administered to a site other than the chest, lungs, chest wall, or chest wall lymph nodes,

cases in which the recorded most clinically significant dose during the first course of treatment was less than or equal to 1000 cGy, or cases in which radiation therapy was not started at or before 180 days from diagnosis were considered to have no radiation.

The adjuvant chemotherapy group was determined by using the "Systemic Surgery Sequence" data item that specifies the temporal relationship of the chemotherapy to the primary surgical procedure for cases diagnosed in 2006. This code was not put in place until 2006, so cases diagnosed between 2003 and 2005 were determined by comparing the number of days elapsed from diagnosis to the date of definitive surgery, and the number of days elapsed from diagnosis to the start of chemotherapy.

Statistics

Management of Clinical Stage IIIA Primary Lung Cancers

The patients were divided into 3 separate cohorts (a priori) to reflect important differences in the availability specific database variables (cohort 1 = 1998 to 2002, cohort 2 = 2003 to 2006, and cohort 3 = 2007 to 2011). More specifically 5-year survival information is only available from 1998 to 2006 (cohorts 1 and 2) and the modified Charlson-Deyo comorbidity index from 2003 to 2011 (cohorts 2 and 3).

Logistic regressions were performed in cohorts 2 and 3 to understand the factors associated with various treatment strategies (surgery, nonsurgical, and no treatment). Patients who were untreated were compared with patients who received nonsurgical treatment (as they were felt to represent more similar patient populations and likely different from the surgical population). In addition, surgically treated patients were

compared with nonsurgically treated patients. The variables considered included the following: race; sex; age; CD score (modified Charlson-Deyo score that included only 3 options, 0, 1. or ≥ 2); histology; year of diagnosis; clinical T stage; Hispanic origin; insurance status; laterality; facility type; facility location; sequence number (refers to patients having multiple cancers; while only patients in whom NSCLC was first cancer were entered into study); crowfly distance of treating facility to patients home; education (% without high school diploma); urban rural status; and income. These variables were first considered in a univariate analysis with those with a p value less than 0.05 being carried forward to the multivariable analysis. Sex of the patient, while not statistically significant, was forced in as it was felt to represent a clinically relevant consideration.

Survival was calculated for each treatment approach first using the Kaplan-Meier method. The survival data are only available for cohorts 1 and 2. We selected cohort 2 to study survival in more detail because it also contained comorbidity data.

A Cox survival analysis was performed using cohort 2. A univariate analysis for correlation with survival was performed using the following variables: treatment approach (surgery alone, surgery with chemotherapy, radiation, or both nonsurgical treatment, or no treatment), race, sex, age, CD score (modified Charlson-Deyo score), histology, year of diagnosis, clinical T stage, Hispanic origin, insurance status, laterality, facility type, facility location, sequence number (refers to patients having multiple cancers, while only patients in whom NSCLC was first cancer were entered into study), crow fly distance of treating facility to patients home, education (% without high school diploma), urban rural status, income.

Variables that demonstrated a significant association with 5-year survival ($p < 0.05$) were evaluated in the multivariable Cox model, and the final model derived by stepwise backward elimination. Missing data were managed by classifying missing information as "unknown" in order to assess potential associations with missing information and outcome.

The mortality associated with laterality in patients undergoing pneumonectomy after receiving induction chemotherapy ± radiation was a predetermined query based on published literature suggesting a difference. Thirty-day mortalities among right and left pneumonectomies were compared using the Fisher exact test. All statistical analyses were performed using SAS version 9.3 (Cary, NC).

Impact of Adjuvant treatment for Microscopic Residual disease

Estimates of overall survival, stratified by pathological stage and margin status, were calculated using the Kaplan-Meier method with log-rank test. Survival in the NCDB is calculated from the time of diagnosis.

Multivariable logistic-regression models were developed to identify predictors of margin status (positive or negative). First, bivariate analysis using the chi-squared test for categorical covariates and one-way analysis of variance (ANOVA) for continuous covariates was used to examine differences by surgical margins status. The variables considered included: year of diagnosis, pathologic T stage, pathologic N stage, Charlson-Deyo Score, age, gender, race, Hispanic origin, insurance status, household income, education level, urban/rural status, "great circle distance" (or the distance between the patient's residence and the hospital that reported the case), facility location, facility type,

laterality, histology, primary site, grade, and surgical procedure. Those variables with a p <0.2, were entered into the logistic regression model. Age, gender, year of diagnosis, Charlson-Deyo Score, and grade, while not statistically significant, were forced in as it was felt to represent a clinically relevant consideration. Logistic regression model data are reported using odds-ratios, 95% confidence intervals, and p-values.

Survival analyses were performed on the cohort of patients with microscopically positive margin (R1) population, as this was felt to be the more homogeneous, and potentially salvageable scenario. Overall survival was also estimated using the Kaplan-Meier method and was stratified by pathological stage and treatment type cohort (No Adjuvant Therapy, Chemotherapy Alone, Radiation Alone, and Chemotherapy + Radiation).

In the microscopically positive (R1) population, stage-stratified adjusted survival analyses were performed to assess the impact of treatment type on overall survival. Cox proportional hazard models were developed in several steps. First, the association between the adjuvant therapy type (No Adjuvant Therapy, Chemotherapy Alone, Radiation Alone, and Chemotherapy + Radiation) and 19 potential confounder variables (year of diagnosis, pathologic T stage, Charlson-Deyo Score, age, gender, race, Hispanic origin, insurance status, household income, education level, urban/rural status, “great circle distance” (or the distance in miles between the patient’s residence and reporting hospital), facility location, facility type, laterality, histology, primary site, grade, and surgical procedure) was examined by bivariate analysis using the chi-square test for categorical covariates or ANOVA for continuous covariates. Variables were inspected for co-linearity and to confirm that none of the variables violated the proportional hazards assumption. Those variables that fit the above criteria and with a p value of less than 0.2

or those chosen based on clinical relevance were entered into the Cox proportional hazards model. Both backwards and stepwise elimination were used in creation of the final model with a significance value set at $p<0.05$ to stay in the model. For clinical relevance, age, year of diagnosis, pathologic T stage, gender, histology, Charlson-Deyo Score, and surgical procedure were forced into the model when necessary. All data elements, except for age, were treated as nominal covariates. The specific cut points were chosen a priori and were based on the distribution of values, not patients. The primary end point was date of death, measured from the date of first diagnosis.

The final Cox proportional hazard model for each stage was used to estimate the relative impacts of adjuvant therapy strategies on 5-year overall survival (OS). Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated in models adjusted for covariates of interest. All analysis was performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). A p-value of <0.05 was set as the threshold for significance.

RESULTS

Management of Clinical Stage IIIA Primary Lung Cancers

Study Population

83,913 clinical stage IIIA NSCLC patients with clinical N2 nodal metastases (cStage III-cN2) were identified in the NCDB from 1998 to 2011, representing 11% of all of the NSCLC cases in the NCDB and 36% of the clinical stage III NSCLC cases. The population was separated into 3 time cohorts (1998 to 2002, 2003 to 2006, 2007 to 2011)

in order to observe temporal trends and to cluster patients with similar complete data, as outlined in the Methods section. The patient and tumor characteristics were very similar across the 3 cohorts (Table 1).

Table 1. Demographics, Tumor Attributes, and Management in 3 Time-Based Cohorts

Variable	Cohort 1 1998-2002	Cohort 2 2003-2006	Cohort 3 2007-2009	p Value
Age (years)				
Mean	67	67	68	0.287
Median	69	68	68	
Interquartile range	15	16	16	
Charlson Deyo score (%)				<0.0001
0	NA	65	59	
1	NA	25	28	
2+	NA	10	13	
Sex (%)				<0.0001
Male	59	57	55	
Female	41	43	45	
Race (%)				<0.0001
White	86	86	85	
Black	11	11	12	
Other	2	2	2	
Unknown	1	1	1	
Insurance status (%)				<0.0001
No insurance	3	3	3	
Private insurance, managed care	32	30	28	
Medicaid	4	5	6	
Medicare	56	58	59	
Other Government insurance	1	2	2	
Unknown	4	2	2	

Table 1. Demographics, Tumor Attributes, and Management in 3 Time-Based Cohorts (cont.)

Variable	Cohort 1 1998-2002	Cohort 2 2003-2006	Cohort 3 2007-2009	p Value
Facility type (%)				<0.0001
Community Cancer Program (CCP)	12	13	13	
Academic/research	26	27	27	
Comprehensive CCP	59	58	59	
Other	3	2	1	
Laterality (%)				<0.0001
Left	35	34	35	
Right	58	60	59	
Midline or bilateral	0	0	0	
Unknown	7	6	6	
Histology (%)				<0.0001
Adenocarcinoma	34	28	36	
Bronchioalveolar	1	1	2	
Squamous cell carcinoma	43	35	40	
Other	22	36	22	
Clinical T stage (%)				<0.0001
1	18	20	22	
2	55	55	52	
3	27	25	26	
Grade (%)				<0.0001
1	3	2	3	
2	17	16	19	
3	37	34	34	
4	5	3	2	
Unknown	38	45	42	

Table 1. Demographics, Tumor Attributes, and Management in 3 Time-Based Cohorts (cont.)

Variable	Cohort 1 1998-2002	Cohort 2 2003-2006	Cohort 3 2007-2009	p Value
Tumor size (%)				<0.0001
<10 mm	1	1	1	
10-19 mm	4	6	9	
20-29 mm	11	13	15	
30-39 mm	14	15	16	
40-49 mm	13	13	14	
50-59 mm	11	11	11	
60+ mm	20	21	23	
Unknown	26	20	11	
Primary site (%)				<0.0001
Main bronchus	7	6	5	
Upper lobe	57	58	59	
Middle lobe	5	4	4	
Lower lobe	23	24	26	
Overlapping lesion	2	2	1	
Lung, NOS	6	6	5	

Accuracy of Nodal Staging of Clinical Stage III-cN2 Patients in the NCDB

The NCDB does not include data on the mechanism by which the clinical stage was determined (i.e., positron emission tomography [PET] scan, mediastinoscopy). We use two strategies were to extrapolate the completeness and accuracy of the clinical mediastinal lymph node evaluation. The first strategy took advantage of the fact that the NCDB captures the number of lymph nodes that are examined or aspirated from a patient. Only nonsurgical patients were studied to avoid confusion between lymph nodes evaluated as a part of the clinical staging process and lymph nodes that were removed at the time of definitive surgical resection. Among cStage IIIA-cN2 patients treated without

surgery, only 22.7% (13,178 of 58,016) had 1 or more lymph node examined pathologically or aspirated. Of note, there was increased use of aspiration (1% in cohort 1 and 8% in cohort 3), likely reflecting the more common use of endobronchial ultrasound in that time span. In patients who are not treated at all, the rate of lymph node evaluation has been relatively stable at over the 3 time cohorts around 17%. It is important to note that the specific nodal region (N1, N2, or N3) is not captured by NCDB.

The second strategy used to assess the clinical staging evaluation was compare the clinical nodal stage (cN2) with the pathologic stage (resulting from a pathologist's review of a therapeutic lung surgery tissue) and assess for "overstaging," or the failure to confirm clinical N2 status by examining the definitive surgical specimens. In order to avoid confusion from potential downstaging as a result of neoadjuvant treatment (i.e., chemotherapy, radiation, or both), this analysis was limited to treatment-naïve (no neoadjuvant) surgical patients. Overall, 56% of treatment-naïve cStage IIIA-cN2 patients were confirmed to have N2 metastases in the surgical specimen cN2→pN2, which increased over the study (48% in cohort 1 and 59% in cohort 3 as shown in Table 2. On the other hand, 33% of treatment-naïve patients appeared to have been overstaged by the clinical exam (cN2→pN0 or pN1). An additional 10% of patients were coded as "NX," seemingly from a lack of nodal tissue at all in the surgical resection specimen.

Table 2. Distribution of Pathologic N Stage Among cStage III-cN2 Patients Undergoing Surgery as First Line of Treatment (no Neoadjuvant Therapy)

Pathologic N Stage	Cohort 1 1998-2002 n=1,748	Cohort 2 2003-2006 n=1,634	Cohort 3 2007-2009 n=3,701	All Cohorts 1998-2009 n=7,803
pN0 (%)	24	20	22	22
pN1 (%)	10	9	11	11
pN2 (%)	48	57	59	56
pN3 (%)	1	1	0	0
pNX (%)	17	13	8	11

Management of cStage IIIA-cN2 Patients

The distribution of management approaches of cStage IIIA-cN2 patients is shown in Table 3; 17% of cStage IIIA-cN2 patients are recorded as being untreated. The majority of patients (69%) were treated nonsurgically, including chemotherapy alone (11% of all cStage IIIA-cN2 patients), radiation alone (14%), or chemoradiation (44%).

Table 3. Management of Clinical Stage III-cN2 NSCLC Over 3 Time Periods

Variable	Cohort 1 1998-2002	Cohort 2 2003-2006	Cohort 3 2007-2011	All Cohorts 1998-2011
Surgical treatment (%)[a]	12	13	17	14
Nonsurgical treatment (%)[b]	72	70	66	69
No treatment (%)	16	17	17	17

[a] Includes patients who only underwent surgery as well as those treated with additional therapies (chemotherapy or radiation), before or after surgery (neoadjuvant or adjuvant).
[b] Includes chemotherapy and radiation, alone or in combination.

Surgery was used in 14% of patients, increasing slightly over the study period from 12% in cohort 1 to 17% in cohort 3. Surgery was performed as the only therapy in 3% of

patients, and in combination with chemotherapy, radiation, or both in 11% (given before or after surgery). The specific surgical procedure was most commonly a lobectomy (73%) followed by pneumonectomy (16%) (Table 4). Over time the use of pneumonectomy appears to have declined (22%, 16%, and 12% in cohorts 1, 2, and 3, respectively). Negative margins were recorded in 86% of patients, a positive margin indicated in 10%, and margins were not evaluable or unknown in 4%. Overall the 30-day mortality was 3.5% and varied by surgical procedure as follows: lobectomy (2.8%), pneumonectomy (7.8%), wedge (3%), and segmentectomy (5%). Pneumonectomy mortality among patients receiving induction chemotherapy or chemoradiation was higher for right pneumonectomy (12.3%, 51 of 363) than for left (4.7%, 18 of 369, p = 0.0001).

Table 4. Extent of Surgical Resection of Clinical Stage III-cN2 Non-Small Cell Lung Cancer Over 3 Time Periods

Variable	Cohort 1 1998-2002	Cohort 2 2003-2006	Cohort 3 2007-2011	All Cohorts 1998-2011
Wedge resection (%)	9	9	10	9
Segmental (%)	2	2	2	2
Lobectomy/bilobectomy (%)[a]	67	73	76	73
Pneumonectomy (%)[b]	22	16	12	16

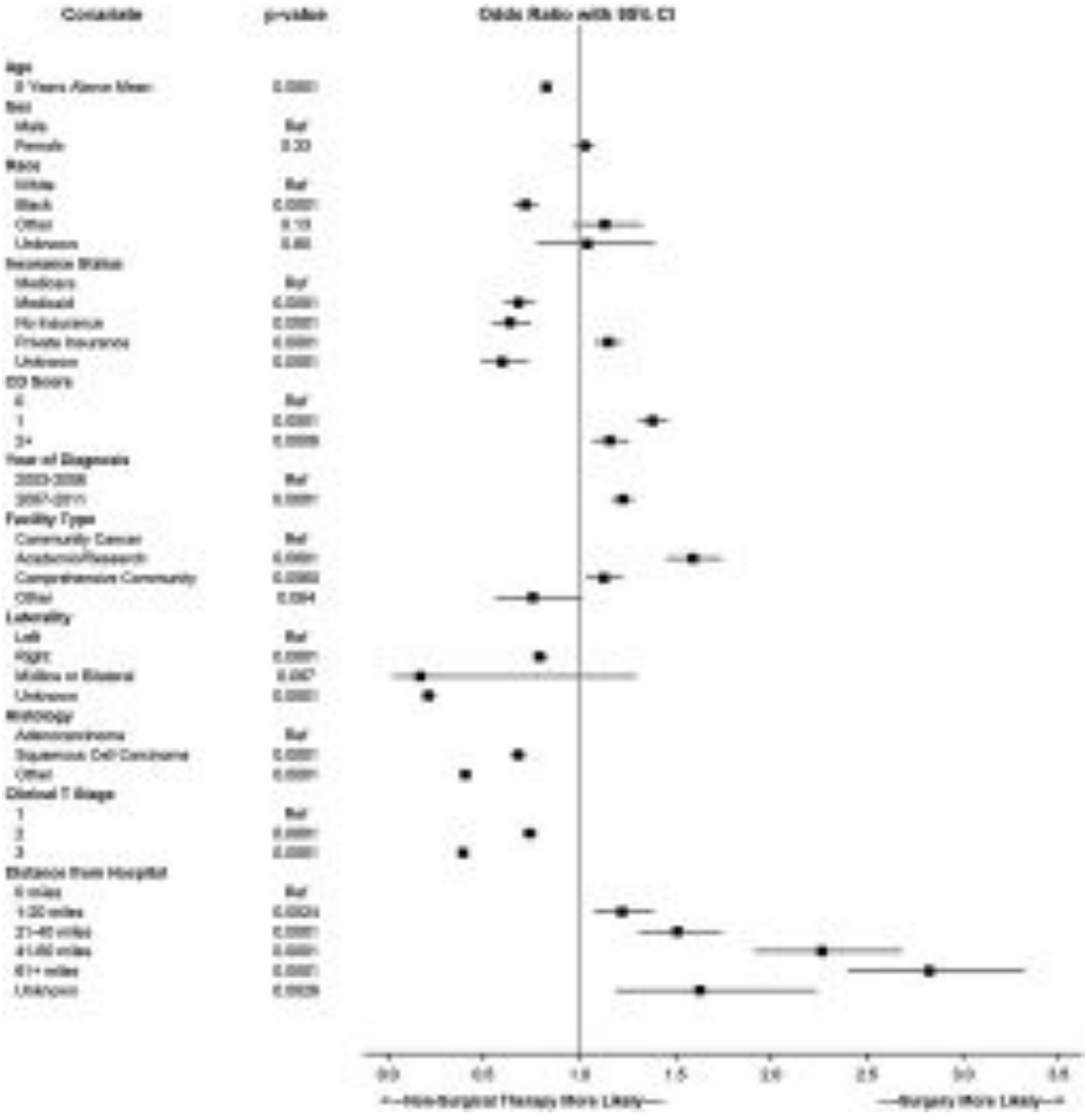
[a] Also includes sleeve resections, or extended lobectomy (chest wall, pericardium, diaphragm).
[b] Also includes extended pneumonectomy (pleura or diaphragm)

Determinates of Treatment

In order to better understand the factors associated with treatment approaches, a logistic regression analysis was performed. Among treated patients, the use of surgery was

significantly increased in the most recent time cohort and those treated at academic centers. On the other hand, African Americans, older patients, right-sided tumors, squamous cell carcinomas, and tumors with advancing T status were less likely to undergo surgery (Figure 1). Surprisingly, increasing number of comorbidities (CD score) was not associated with less frequent use of surgery.

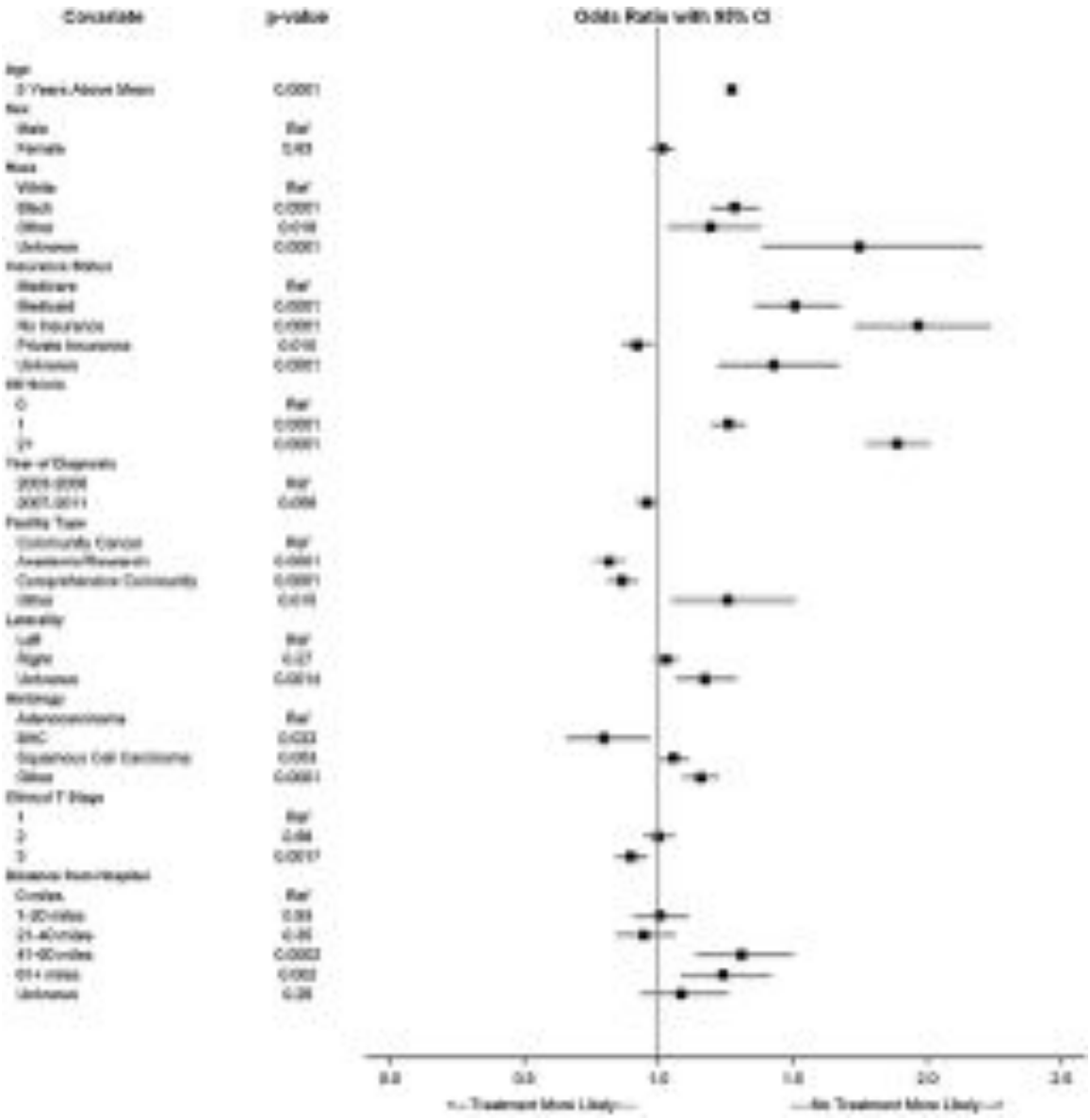
Figure 1. Forest plot of logistic regression comparing clinical stage IIIA-cN2 patients who were treated surgically to those treated with nonsurgical approach (chemotherapy, radiation, or chemotherapy + radiation). (CI = confidence interval.)



The NCDB also captures the reason why surgery was not performed. The most common reason listed for no surgery among patients treated with chemotherapy, radiation, or both was “Surgery was not part of the planned first course of treatment” (85%). In 3% of nonsurgically treated patients, surgery was actually recommended but the patient either refused treatment (510 patients) or surgery was not performed for other unknown reasons (1,063 patients); 45 patients died prior to planned or recommended surgery.

In order to better understand the untreated population, a logistic regression was performed comparing untreated patients to those who received nonsurgical treatment (Figure 2). Several factors were associated with receiving no treatment, including advancing age, nonwhite race, insurance status (“no treatment” was more likely with Medicaid or no insurance), increasing comorbidities, right sided tumors, treatment at community cancer centers, advanced T status, and increasing distance between the patient and the medical center.

Figure 2. Forest plot of logistic regression comparing clinical stage IIIA-cN2 patients who were untreated to those who were treated with nonsurgical approach (chemotherapy, radiation, or chemotherapy + radiation). (CI = confidence interval.)



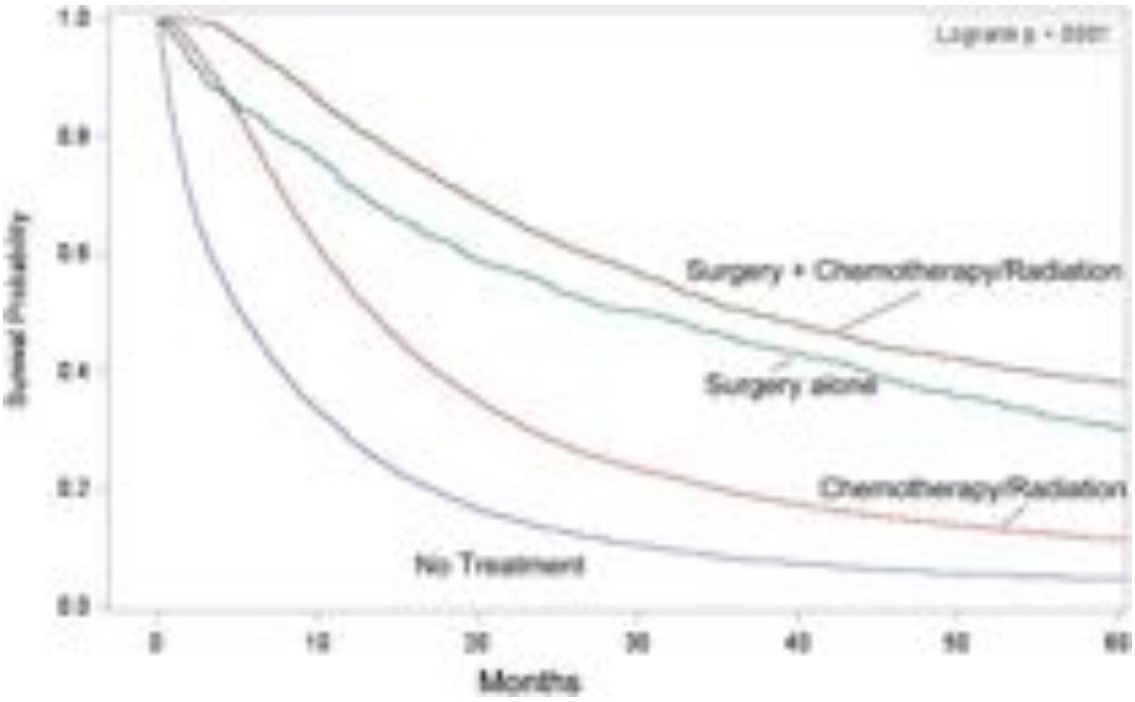
Survival of cStage IIIA-cN2 in the NCDB

A limited temporal analysis of survival was performed comparing cohorts 1 and 2 (survival information unavailable for cohort 3). The entire cStage IIIA-cN2 population

fared better in cohort 2 (14% 5-year survival) compared with cohort 1 (10%). The survival increased for each of the general treatment strategies from cohort 1 to cohort 2 (surgery 28% to 36%, nonsurgical treatment 9% to 11%, no treatment 3% to 5%).

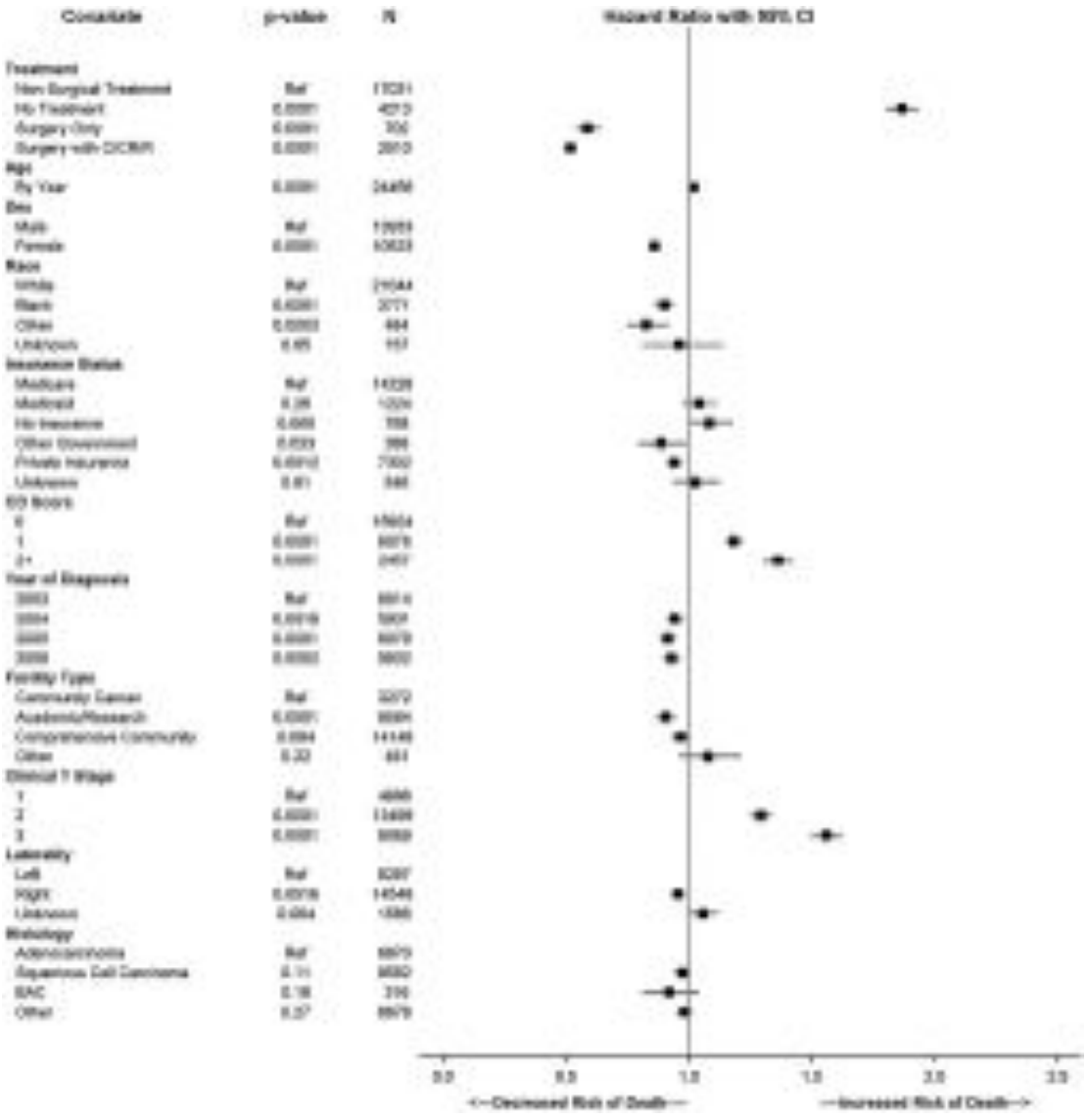
Because only cohort 2 has both survival information and comorbidity data, a more detailed analysis was performed on these patients stratifying survival according to specific treatment approaches. The 5-year survival by Kaplan-Meier survival curves according to treatment is as follows: untreated (4.7%), nonsurgical treatment (11.4%), surgery alone (30%), and surgery with additional chemotherapy, radiation, or both (38%) (Figure 3).

***Figure 3*.** Kaplan-Meier survival curves of clinical stage IIIA-N2 patients in cohort 2 (diagnosed 2003 to 2006) according to the treatment received.



To further understand factors associated with survival in the cStage III-cN2 population, a Cox multivariable analysis was also performed on cohort 2 (Figure 4). Several variables appeared to correlate with survival, most notably including the treatment approach, which mirrored findings above. Other factors associated with an improved survival included the following: female sex; nonwhite race; private insurance; the absence of comorbidities; treatment at an academic medical center; lower clinical T stage; and left-sided tumors.

Figure 4. Forest plot of Cox survival analysis of clinical stage IIIA-cN2 patients in the National Cancer Database.



Impact of Adjuvant treatment for Microscopic Residual disease

Prevalence and Impact of Incomplete Resections

A total of 54,512 patients who underwent resection of a treatment-naïve NSCLC between 2003 and 2006 were identified. Some residual disease was identified in 3,102 (5.7%) of surgical procedures, including 1,688 (3.1%) with microscopically positive (R1) margins and 181 (0.33%) with macroscopically positive (R2) margins. An additional 1,233 (2.3%) were coded as "residual disease not otherwise specified (NOS)."

Overall 5-year survival was determined for each of the pathologic stage groups (I,II,III) according to margin status (Table 5). The presence of a positive margin was associated with a decreased 5-year survival for each pathologic stage.

Table 5. Stage – specific unadjusted 5 Year overall survival by surgical margin status

	Surgical Margins			
Pathologic Stage	**No Residual Tumor** (51,410)	**Microscopic Residual** (1,688)	**Macroscopic Residual** (181)	**Residual Tumor NOS** (1,233)
I	62%	37%	22%	45%
II	41%	29%	34%	27%
III	33%	19%	12%	13%

NOS, Not Otherwise Specified.

Predictors of incomplete resection

In order to better understand the factors influencing margin status, a logistic regression was performed comparing patients with negative (R0) and positive margins (R1, R2, or

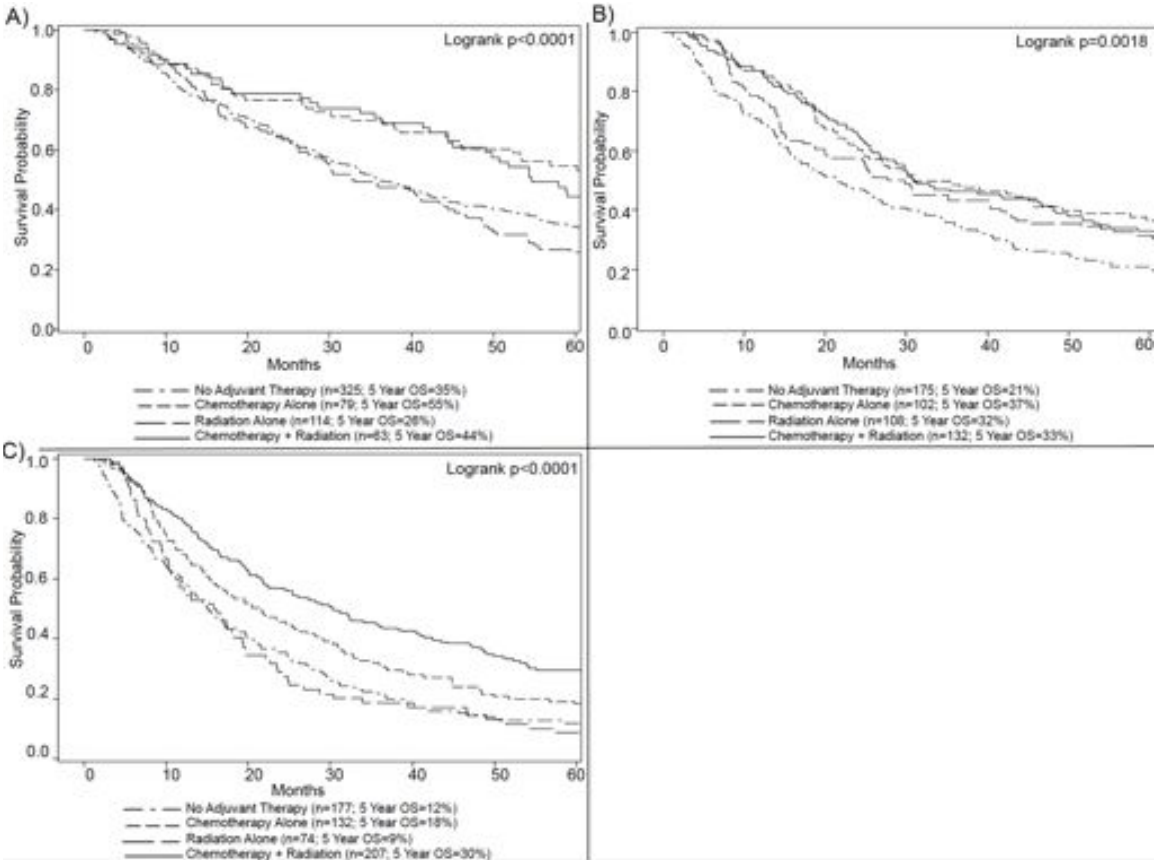
residual tumor, NOS). Advancing pathologic "T" and "N" stage were associated with increased likelihood of positive margins ("T" stage 2 versus 1 OR 2.448, 95% CI [2.209 to 2.713] p<0.0001 and "N" stage 2 versus 1 OR 2.334, 95% CI [2.122 to 2.568] p<0.0001), as was the use of wedge resection compared to anatomic resections (OR 2.365, 95% CI [2.127 to 2.63] p<0.0001). On the other hand, Academic/Research hospitals were associated with a lower incidence of positive margins than Community Cancer hospitals (OR 0.782, 95% CI [0.681 to 0.899] p=0.0005).

Stage-Specific Survival in R1 patients According to Adjuvant Treatment Strategy

Conceptually, microscopic residual disease (R1) is thought represent a salvageable scenario in which additional therapy could contain what was presumed to be locoregionally confined NSCLC. Therefore the subsequent multi-variable adjusted analyses were focused on R1 patients and excluded macroscopically positive margins or patients with "residual disease, not otherwise specified". In addition, because several stage-specific considerations exist for adjuvant therapy among completely resected NSCLC, the R1 patients were analyzed separately by stage (I, II, and III).

A total of 581 stage pI NSCLC patients with an R1 resection were evaluated. The unadjusted 5-year survival with no adjuvant therapy was 35%. The addition of either chemotherapy alone (5-year survival = 55%;p=0.0009), or chemotherapy + radiation (5 year survival = 44%;p=0.05) were associated with a superior survival. The addition of radiation alone was not (5-year survival = 26%;p=0.0399) (Figure 5A).

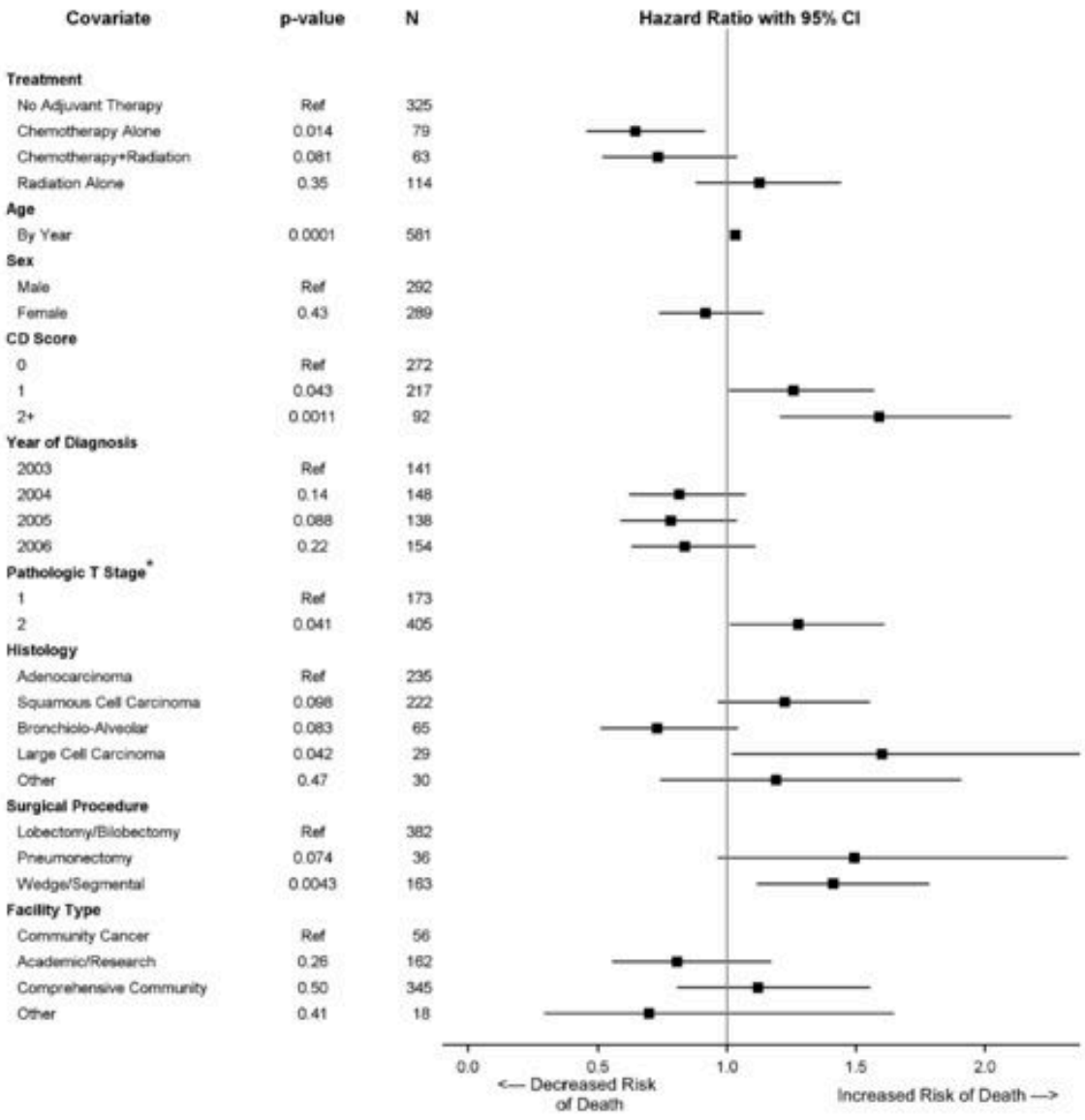
Figure 5. Kaplan Meier survival analysis demonstrating 5 year overall survival of patients with a microscopically positive margin according to adjuvant strategy for A) Pathologic stage I, B) Pathologic stage II, and C) Pathologic stage III NSCLC.



In attempt to adjust for heterogeneity in the stage pI cohort, a Cox proportional hazards model was created (variables and strategy given in METHODS section) to evaluate predictors of survival. Advancing age, increasing comorbidities, pT2 status (compared to T1), and the use of sublobar resection were associated with a significant decrease in survival (Figure 6). Compared to "no adjuvant therapy," postoperative chemotherapy alone was the only adjuvant strategy to be associated with a significantly superior outcome (HR 0.644, 95% CI [0.454 to 0.915] p=0.014, while chemotherapy + radiation (HR 0.732, 95% CI [0.516 to 1.039] p=0.081) trended towards a better outcome.

Interestingly, radiation alone was not associated with an improvement in survival over "no adjuvant therapy" in this multivariable model (HR 1.125, 95% CI [0.878 to 1.442] p=0.35 (Figure 6).

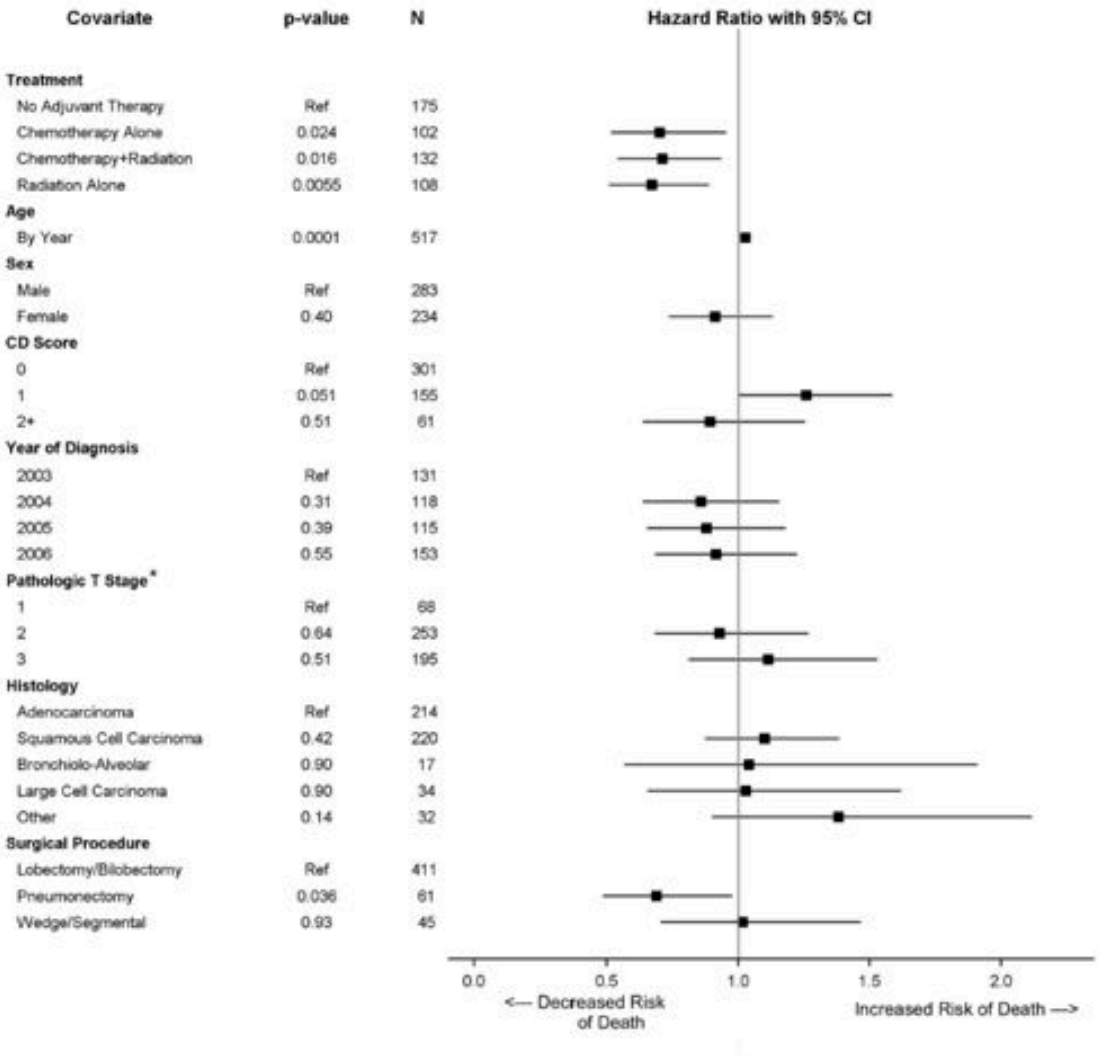
Figure 6. Forest plot demonstrating a Cox proportional hazards model for stage pI patients. *3 cases with unknown pathologic T stage were excluded from the table.



A total of 517 stage pII patients with R1 resection were identified. The unadjusted 5-year survival with no adjuvant therapy was 21%. The addition of chemotherapy alone (5-year survival = 37%;p=0.0023), or chemotherapy + radiation (5-year survival = 33%;p=0.0013), or radiation alone (5-year survival 32%;p=0.0441) were all associated with significantly superior survival (Figure 5B).

In an adjusted analysis of R1-resected stage pII patients, advancing age was a predictor of poorer survival, while the association between comorbidities, advancing "T" status (pT2 or pT3 status compared to T1), and extent of resection performed (i.e. lobectomy vs. wedge) and survival was less clear (Figure 7). Chemotherapy alone (HR 0.701, 95% CI [0.516 to 0.954] p=0.024), chemotherapy + radiation (HR 0.711, 95% CI [0.54 to 0.937] p=0.016), and radiation alone (HR 0.672, 95% CI [0.508 to 0.89] p=0.0055) were all associated with a better outcome than no adjuvant therapy (Figure 7).

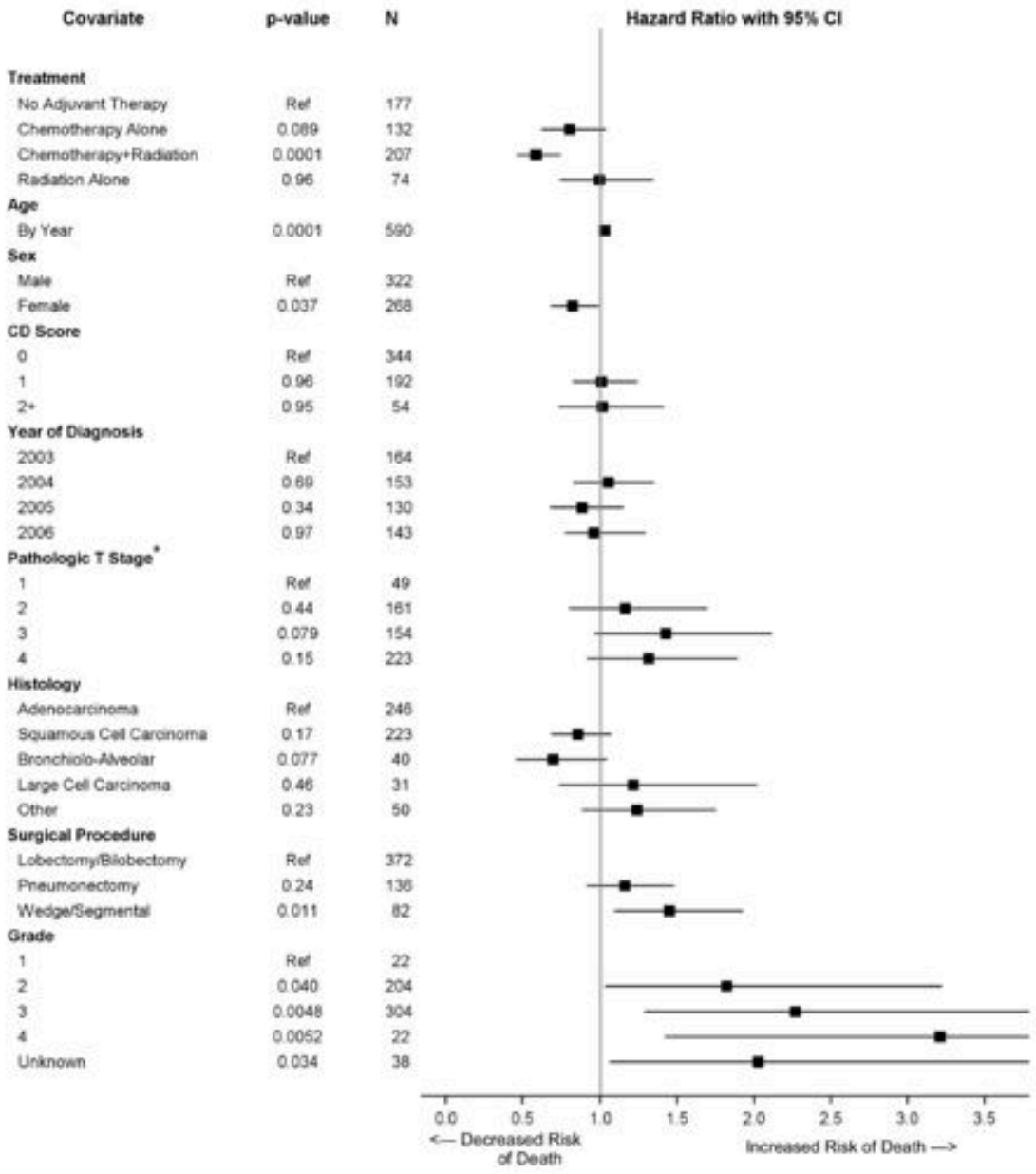
Figure 7. Forest plot demonstrating a Cox proportional hazards model for stage pII patients. *1 case with unknown pathologic T stage was excluded from the table.



A total of 590 stage pIII patients with R1 resection were evaluated. The unadjusted 5-year survival with no adjuvant therapy was 12%. The addition of chemotherapy alone (5-year survival = 18%;p=0.0187), or chemotherapy + radiation (5-year survival = 30%;p<0.0001), were associated with a superior survival. The addition of radiation alone was not (5-year survival 9%;p=0.9441) (Figure 5C).

In an adjusted analysis of R1-resected stage pIII patients, advancing age and the use of sublobar resection were again associated with a significant decrease in survival (Figure 8). Compared to “no adjuvant therapy,” postoperative chemotherapy + radiation was the only adjuvant strategy to be associated with a significantly superior outcome (HR 0.583, 95% CI [0.459 to 0.742] $p<0.0001$), while chemotherapy alone (HR 0.797, 95% CI [0.614 to 1.035] $p=0.089$) trended towards a better outcome. Radiation alone was not associated with an improvement in survival (HR 0.992, 95% CI [0.992 to 1.344] $p=0.96$).

Figure 8. Forest plot demonstrating a Cox proportional hazards model for stage pIII patients. *3 cases with unknown pathologic T stage were excluded from the table.



DISCUSSION

With a population of over 80,000 in the cStageIIIA-cN2 NSCLC study and a population of over 3000 patients in the positive margins study, the NCDB demonstrates its invaluable use as a resource to investigate these subsets and others like them.

Management of Clinical Stage IIIA Primary Lung Cancers

As with any investigation concerning a clinically staged population, a key issue becomes the accuracy of the clinical stage IIIA-cN2 designation. Somewhat surprisingly, the clinical staging evaluation of nonsurgical patients did not involve the examination of lymph node tissue by a pathologist in the majority of patients (77%). This implies that only noninvasive staging was used to establish N2 status in the majority of nonsurgically managed patients. This is concerning because noninvasive staging modalities are notorious for overestimating mediastinal lymph node metastases. For example, PET and PET-computed tomographic (CT) scans have a 25% false positive rate in the mediastinum, and CT scan has over a 40% false positive rate for N2 disease.[6] Therefore, it is possible that a significant portion of the clinical N2 patients did not in fact have N2 disease (potentially rendering them as stage I or stage II). The fact that the treatment-naïve surgical patients were only confirmed as having N2 disease 56% of the time further supports this assertion that NCDB patients were prone to overstaging by the clinical staging evaluation. While the role of surgery in patients with stage IIIA NSCLC may be less clear, surgery has a much more supported role in earlier stage cancer.[5] As a result, the overstaging of patients may in fact be causing patients to be directed toward less effective treatment approaches. Therefore, irrespective of the preferred stage IIIA

treatment strategy, in order to optimize care, all patients should be staged with the same degree of diligence.

The management of cStage IIIA-cN2 within the NCDB reflects a trend away from surgery among case series, published trials, and national treatment guidelines.[4,19] Several factors associated with the use of surgery illustrate clear tendencies by patients, providers and insurers. Perhaps more concerning are the predictors of "no treatment," as they could potentially reflect important health care disparities. The current study identified race, insurance status, the type of facility, and distance between the facility and the patient all being associated with a likelihood of not being treated at all. Because no treatment is indisputably less effective than treatment, this could translate into worse outcomes in the populations affected by these variables.

Among patients who did undergo surgery, the surgical outcomes in the NCDB compare well to the published series. More specifically, the 30-day mortality for lobectomy (2.8%) is well within the published range for primary lung cancer surgery[7,20] but remains a bit higher than that of Society of Thoracic Surgeons (1.8%).[21] Of interest, a right-sided pneumonectomy after induction chemotherapy, with or without radiation, was associated with a higher 30-day mortality than a left-sided (12% vs 5%). The importance of laterality for postinduction pneumonectomy has been the subject of ongoing debate, with some studies finding a higher mortality with right-sided pneumonectomy[22] while others have challenged this concept.[21,23]

The 5-year survival of the entire cStageIIIA-cN2 population in the NCDB (14%) is on par with that of the International Association for the Study of Lung Cancer's staging

project (17%).[24] The outcomes appear to be best for patients treated with surgery, particularly those who were treated with a multimodality approach (including chemotherapy, radiation, or both). This almost certainly implies patient factors are at play that go beyond the degree to which the NCDB captures. As such, we would not assume that this data indicates a superiority of surgery-based treatment approaches. That being said, the 5-year survival of surgery-treated patients compares well with clinical trials that have studied curative-intent treatment of NSCLC and paints an encouraging picture for surgically managed stage IIIA NSCLC in the United States.[4]

There are several limitations to this study. The first being the possibility that important elements of the patient's care took place at hospitals that are not accredited by the Commission on Cancer (CoC), and therefore are not captured by the NCDB. It is the responsibility of the submitting CoC hospital to research all aspects of care, including elements that occurred at non-CoC hospitals, but this does represent a vulnerability of the NCDB for incomplete data. In addition, the treatment within this stage cohort likely reflects aspects of the patients and tumors that are beyond the detail captured by the database, and therefore treatment-associated outcomes may not be comparable.

The NCDB represents an invaluable resource for the study of clinical stage III-cN2 NSCLC. The extent to which the mediastinum has been accurately staged is unclear as invasive mediastinal staging appears to have been used sparingly in the nonsurgically managed patients, and just over half of the treatment-naïve surgical patients were confirmed to have N2 disease. Surgery is used less frequently in clinical stage IIIA-cN2 disease in the NCDB, but is associated with encouraging outcomes. Further study is warranted to clarify the degree to which overstaging is directing patients away from

surgery in the United States.

Impact of Adjuvant treatment for Microscopic Residual disease

The 3,102 cases of positive margins, to the best of our knowledge, represent the largest cohort of incompletely resected NSCLC patients reported in the literature. The incidence of incompletely resected NSCLC in the NCDB (5.7%) is well within the range of previous reports (2 - 17%).[7-10,12,25] Furthermore, the positive margin patients in the NCDB experienced a stage-specific compromise in survival (relative to completely resected patients), that is similar to other longitudinal NSCLC studies.[9,11]

Several factors identified to predict positive margins in the NCDB (advancing pathologic T and N stages, and use of sublobar resection) echo the findings of other reports.[9,26] We did note that positive margins were less frequent at academic centers. This would be consistent with surgical studies that have found academic centers to be associated with improvements in surgical quality for lung cancer.[20]

Adjuvant therapy appears to rescue a fraction of R1 patients from the compromised survival associated with residual disease. A number of stage-specific nuances to the efficacy of adjuvant therapy for incompletely resected NSCLC were identified. For pathologic stage I NSCLC with R1 resection, chemotherapy appeared to benefit patients while radiation alone did not. This is a bit counterintuitive, as pathologic stage I tumors are presumed to be confined to the lung parenchyma, and a positive margin would represent a risk for local failure, which would theoretically be modifiable by additional local therapy (which radiation represents). This finding contradicts several smaller studies that have suggested a role of adjuvant radiation for positive margins.[25,27,28] The

American College of Chest Physicians currently recommends radiation alone in the setting of a positive margin for stage I NSCLC.[5] On the other hand, the current study is not alone in failing to identify a survival advantage with adjuvant radiation.[10,12,25,29]

Alternatively, the lack of significant survival advantage with radiation alone may reflect an artifact or limitation of the dataset in the NCDB. The number of patients treated with radiation alone is not large (n = 114) and it is possible that the subgroup survival was influenced by factors not captured by the NCDB data fields (e.g. lung function). It is also possible that the patient survival is dominated by other cancer-specific risk factors. For example, subgroup analysis of an adjuvant NSCLC chemotherapy trial, CALGB 9633 suggested that tumors greater than 4cm benefit from adjuvant chemotherapy.[30] 34% of the R1 resections for stage pI NSCLC that were treated with postoperative radiation alone, involved tumors that were over 4cm (and potentially could have benefitted from chemotherapy based on size alone).

In patients with stage II disease, all three forms of adjuvant therapy appeared to be similarly superior to surgery alone. Unlike stage I patients, postoperative radiation alone was beneficial for incompletely resected stage II. Of the 108 stage II patients treated with radiation alone, 58 were "N0", potentially representing a subgroup that was containable with local therapy. However, the discrepant outcome with radiation alone in stage I and II in this regard is unclear.

For stage III patients with a microscopically positive margin, the administration of chemotherapy + radiation was associated with the best outcomes. Interestingly, the outcome of R1 patients treated with chemotherapy and radiation (30%) is actually quite similar to completely resected

(R0) pathologic stage III patients (5-year survival of 33% in Table 5). In some regards, the best outcome being seen in R1- resected stage pIII patients treated with adjuvant chemotherapy and radiation is not surprising, as trimodality therapy has emerged as the optimal approach in completely resected stage pIII NSCLC.[31,32]

The principle limitation of the study is the assumption that patient differences in each treatment cohort were adjustable using the NCDB data fields. More specifically, there are likely patient and tumor attributes that influenced the use of post-operative therapy that are not captured by the NCDB (e.g. pulmonary function). These concerns grow as the stage increases, because the evolving standard of care for R0 patients would have been for adjuvant chemotherapy for stage II and chemoradiation for stage III.[31,32] Therefore many of the stage II and III treatment cohorts could be considered deviations from the standard of care. These deviations may have been justified but could reflect patient characteristics not captured by NCDB that also influenced survival. It is worth noting that although adjuvant chemotherapy has demonstrated an absolute increase 5-year survival benefit of 5% for NSCLC, many of the chemotherapy containing adjuvant cohorts experienced two to three times this benefit. Therefore the effect of adjuvant chemotherapy in the R1 patient cohorts is not entirely explained by the generic benefit of adjuvant chemotherapy for surgically managed NSCLC.

It is also important to note that the NCDB does not capture patients in our population who underwent re-resection after their initial R1 resection, which is currently recommended by the National Comprehensive Cancer Network for stage I or stage II NSCLC.[13] Additionally, the NCDB does not capture causes of death or sites of recurrence, fields that would have been helpful to evaluate efficacy of adjuvant treatment.

Positive surgical margin therefore, portends a substantial drop in stage-specific survival in NSCLC. There does appear to be an advantage to adjuvant therapy, with the most consistent outcomes across all pathologic stages being associated with chemotherapy + radiation. Further study is warranted.

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